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Public Assessment Report

Scientific discussion

Olopatadine UNIMED PHARMA 1mg/ml

olopatadine hydrochloride

SK/H/0202/001/DC

Date: May 2020

This module reflects the scientific discussion for the approval of Olopatadine UNIMED PHARMA 1mg/ml, eye drops solution. The procedure was finalised at 17.1.2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for **Olopatadine UNIMED PHARMA 1mg/ml, eye drops solution**, from **Unimed Pharma spol.s.r.o.**.

The product is indicated for:
Treatment of ocular signs and symptoms of seasonal allergic conjunctivitis.
Olopatadine UNIMED PHARMA is indicated in adults, adolescents aged 12 to 18 years and children aged 3 to 12 years.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC."

II. QUALITY ASPECTS

II.1 Introduction

Olopatadine UNIMED PHARMA 1mg/ml, eye drops, solution (eye drops) is clear, colourless solution, practically free from visible particles, with a pH between 6.5 - 7.5, and an osmolality of 280 - 320 mOsm/kg.

II.2 Drug Substance

INN	Olopatadine hydrochloride. Olopatadine HCl is not described in the Ph. Eur., but it is described in USP.
Molecular Formula	$C_{21}H_{23}NO_3$. HCl
Appearance	White crystalline powder, odourless
Solubility	Highly soluble in formic acid, slightly difficult to be soluble in water or in ethanol (95), hardly soluble in acetic acid (100), highly difficult to be soluble in acetonitrile, almost not soluble in acetic anhydride or in diethyl ether.
Melting point	About 250 °C (with decomposition)
Activity	It is an antiallergic/antihistaminic drug for topical ocular use. The effects of the compound on release of proinflammatory mediators (histamine, tryptase and prostaglandin D2) from monodispersed human conjunctival mast cells were assessed. The results showed that olopatadine is useful in the treatment of ocular allergic diseases.
Manufacturing:	An ASMF procedure is followed for the drug substance.

All results of stability studies are in compliance with specifications.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients are Ph. Eur. The compatibility between the drug substance and excipients in the drug product is proved by the stability tests.

To avoid the use of preservative is olopatadine ophthalmic solution packed in Novelia packaging system. The Novelia integrity system prevents inner solution against bacterial contamination over the duration of treatment.

The manufacturing process development of the drug product is based on own Unimed Pharma‘s experience with manufacturing simple sterile water solutions. The active substance is along with excipients dissolved in sterile water. After complete dissolution, bulk solution is filtered via sterilisation filter and aseptically filled into sterile plastic primary packaging containers. Sterilisation process and filling process are performed under grade A of clean spaces. The manufacturing process development and optimization of the drug product have been sufficiently described.
The release and shelf life specifications of the drug product have been provided. Analytical methods have been sufficiently described. The validation of HPLC methods, UV/VIS method and method for sterility have been provided.
According to satisfactory long-term stability data, the proposed shelf life of 24 months is acceptable.
Based on the presented stability results, the storage conditions “Do not store above 25 °C” is acceptable.

Because “significant change” occurred during accelerated stability testing, additional testing at the intermediate storage condition was required. The manufacturer declares that immediately first product commercial batch will be set up for stability study including intermediate storage condition. The applicant’s commitment is acceptable

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of olopatadine are well known. As olopatadine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is acceptable.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The applicant provided the ERA assessment with the calculated PECsw which was well below the threshold value 0,01 microg/Land. The log Kow value was evaluated based on experimental data at -0.565. Olopatadine HCL is not a PBT substance as log Kow does not exceed the limit 4.5.

IV. CLINICAL ASPECTS

IV.1 Introduction

Olopatadine is a potent selective antiallergic/antihistaminic agent that exerts its effects through multiple distinct mechanisms of action. It antagonises histamine (the primary mediator of allergic response in humans) and prevents histamine induced inflammatory cytokine production by human conjunctival epithelial cells.

Pharmacological classification: ophthalmologicals; decongestant and antiallergics; other antiallergics.
ATC code: S01GX09

IV.2 Pharmacokinetics

Biowaiver
In support of this hybrid application no clinical efficacy studies were performed by the MAH. Olopatadine UNIMED PHARMA 1mg/ml eye drops, solution is olopatadine hydrochloride packed in a Novelia multidose closing tip system which avoids the need for preservatives. The Novelia integrity system prevents inner solution against bacterial contamination over the duration of the treatment.
Olopatadine UNIMED PHARMA 1 mg/ml eye drops, solution contains the same active substance at the same concentration and the same excipients as the reference product OPATANOL 1 mg/ml eye drops, solution. Essential similarity with the reference product is based on the comparative quality attributes of the product. There are no new excipients or new salts. Also the pH value, osmolality, density, and droplet size are similar. Since there are no changes in the composition, except preservative substance (benzalkonium chloride) of the hybrid product in comparison to the reference product which would change the absorption or tolerability of olopatadine, no impact on efficacy is expected. Discussion concerning relevance of difference in viscosity between solutions containing benzalkonium chloride and benzalkonium chloride –free solutions took place during the assessment. References with clinical studies comparing preservative and preservative-free solutions to support the claim that absence of benzalkonium chloride will not lead to different efficacy were provided. Totality of data shows that removal of benzalkonium chloride from an ophthalmic formulation should not lead to change in terms of efficacy.

The applicant asks for a biowaiver based on similarity with the reference medicinal product. Such approach to waive a BE study is acceptable since plasma levels are not relevant for local efficacy and the test product is of the same type of solution and contains the same concentration of the same active substance as the medicinal product currently approved.

IV.3 Pharmacodynamics

Olopatadine is a potent selective antiallergic/antihistaminic agent that exerts its effects through multiple distinct mechanisms of action. It antagonises histamine (the primary mediator of allergic response in humans) and prevents histamine induced inflammatory cytokine production by human conjunctival epithelial cells. Data from *in vitro* studies suggest that it may act on human conjunctival mast cells to inhibit the release of pro-inflammatory mediators. In patients with patent nasolacrimal ducts, topical ocular administration of olopatadine was suggested to reduce the nasal signs and symptoms that frequently accompany seasonal allergic conjunctivitis. It does not produce a clinically significant change in pupil diameter.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Olopatadine UNIMED PHARMA 1 mg/ml.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary table of safety concerns as approved in RMP

Important identified risks	
Important potential risks	• Corneal damage
Missing information	• Use during pregnancy • Use during breastfeeding

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

The user testing package leaflet was conducted in Slovak language and the report is dated 30.1.2018. The test results were translated into English.

In total 23 participants were included in testing. 1 pilot and 2 main testing rounds were conducting and participants were posed 18 questions to key safety issues and addition 1 question concerning the overall impression of the PIL.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

According to the guideline CPMP/QWP/122/02, rev 1 corr, the additional testing at the intermediate storage condition should be conducted. The relevant data should be presented.
The drug product manufacturer declares that the intermediate stability study will be set up on first commercial batch of drug product. The applicant's commitment is acceptable.

The benefit risk of this medical product was considered positive. Therefore the RMS and CMSs recommended approval of Olopatadine UNIMED PHARMA 1mg/ml eye drops, solution.